Remarks/Arguments:

Minor changes are made to the specification to insert sequence identifiers and to combine the two reference lists. Claims 3, 6, 14, 19, and 26-31 are canceled without prejudice. Claims 1, 7, 9, 13, and 15-18 are amended. Amended claim 1 is a combination of original claims 1, 3, and 6; amended claim 7 is a combination of original claims 6 and 7; amended claim 13 is a combination of original claims 13 and 14, excluding "tissue sample;" amended claim 15 is a combination of original claims 13 and 15, excluding "D10S197;" amended claim 16 is a combination of original claims 13 and 16, excluding "P16, KRAS, BRAF;" amended claim 17 is a combination of original claims 17 and 19, excluding "tissue sample;" amended claim 18 is a combination of original claims 17 and 18, excluding "breast" cancer. Claim 9 is amended to correct a typographic error. No new matter is introduced.

Claims 1-2, 4-5, 7-13, 15-18, and 20-25 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

OBJECTION TO THE SPECIFICATION

The specification is objected to for failing to provide a sequence listing. Applicants submit herewith a Sequence Listing in computer readable form as required by 37 C.F.R. §1.824. In addition, Applicants submit an initial Sequence Listing as required under 37 C.F.R. §1.823(a) and a statement under 37 C.F.R. §1.821(f). Applicants respectfully request entry of the paper copy and computer readable copy of the Sequence Listing filed herewith for the instant application. No new matter is introduced. Withdrawal of the objection is respectfully requested.

INFORMALITIES

The Examiner suggested that all references be placed at the end of the disclosure. Accordingly, Applicants have combined the two lists of references and placed them at the end of the disclosure.

CLAIM REJECTIONS UNDER 35 USC § 102

(1) Claims 13-14 and 17-25 are rejected as being anticipated by Yang et al. (2002) Clinical Cancer Research 8:2890-2893 ("Yang"). Claims 14 and 19 have been canceled without prejudice and will not be discussed below.

Amended claim 13 is directed to a method of detecting a combination of LOH and DNA hypermethylation in a serum or plasma sample from a subject. Likewise, amended claim 17 is directed to a method of detecting cancer by detecting one or more DNA markers in a serum or plasma sample from a subject, wherein a combination of LOH and hypermethylation of the markers is indicative of cancer in the subject. In contrast, Yang describes detection of LOH and hypermethylation of the FHIT gene in breast cancer tissue samples (the paragraph bridging pages 2890 and 2891). Because Yang does not disclose detection of LOH and DNA hypermethylation in a serum or plasma sample, it cannot anticipate amended claim 13 or 17.

Amended claim 18 is directed to a method of detecting cancer by detecting one or more DNA markers in a sample from a subject, wherein a combination of LOH and hypermethylation of the markers is indicative of melanoma, neuroblastoma, colorectal, or prostate cancer in the subject. As mentioned above, Yang describes detection of LOH and hypermethylation of the FHIT gene in breast cancer tissue samples. Because Yang does not disclose association of LOH and DNA

hypermethylation with melanoma, neuroblastoma, colorectal, or prostate cancer, it cannot anticipate amended claim 18.

Claim 20 is directed to a method of staging cancer by detecting one or more DNA markers in a sample from a subject suffering from cancer, wherein a combination of LOH and hypermethylation of the markers is indicative of an advanced stage of the cancer in the subject. Claim 23 is directed to a method of prognosing cancer by detecting one or more DNA markers in a sample from a subject suffering from cancer, wherein a combination of LOH and hypermethylation of the markers is indicative of a poor prognosis of the cancer in the subject. Contrary to the Examiner's belief, Yang does not teach the association of a combination of LOH and DNA hypermethylation with either an advanced cancer stage or a poor cancer prognosis. In particular, Yang states that aberrant Fhit expression has been associated with pathogenesis and prognosis of various tumors (page 2892, right column, lines 1-3); however, some tumors with reduced Fhit expression have no LOH or methylation, and other mechanisms such as splicing abnormality should be considered (page 2892, right column, lines 25-28). Since Yang suggests no link between a combination of LOH and DNA hypermethylation and an advanced cancer stage or a poor cancer prognosis in some tumors, it cannot anticipate claim 20 or 23.

In view of the foregoing, claims 13, 17-18, 20, and 23 are novel over Yang. Claims 21-22 (dependent from claim 20) and 24-25 (dependent from claim 23) are not anticipated by Yang for at least the same reasons. Applicants respectfully request that the rejections be withdrawn.

(2) Claims 13-15, 17, 19-20, 22-23, and 25 are rejected as being anticipated by Kondo et al. (2000) Hepatology 32:970-979 ("Kondo"). Claims 14 and 19 have been canceled without prejudice and will not be discussed below.

As mentioned above, amended claims 13 and 17 require detecting a combination of LOH and DNA hypermethylation in a serum or plasma sample from a subject. In contrast, Kondo describes detection of LOH and DNA hypermethylation in non-cancerous and cancerous liver tissue samples (page 971, left column, lines 30-33 and 46-48). Because Kondo does not disclose detection of LOH and DNA hypermethylation in a serum or plasma sample, it cannot anticipate amended claim 13 or 17.

Amended claim 15 is directed to a method of detecting a combination of LOH and DNA hypermethylation in a sample from a subject, wherein the LOH is indicated by one or more DNA markers that include D1S228, D8S321, D4S175, D4S1586, D5S299, D8S133, D8S261, D8S262, D8S264, D9S171, D10S591, D10S532, D14S51, D14S62, D15S127, D16S421, D16S422, D17S796, D17S849, D17S855, D18S58, D18S61, or D18S70. Because Kondo does not disclose any of the DNA markers recited in amended claim 15, it cannot anticipate amended claim 15.

As mentioned above, claims 20 and 23 require the association of a combination of LOH and DNA hypermethylation with an advanced cancer stage and a poor cancer prognosis, respectively. Contrary to the Examiner's belief, Kondo does not teach such association. In particular, while Kondo compares LOH and DNA hypermethylation in normal liver tissues, non-cancerous liver tissues, and hepatocellular carcinoma (page 974, Table 3), it does not compare LOH and DNA hypermethylation in cancerous liver tissues of different cancer stages or different cancer prognoses, and therefore suggests no link between a combination of LOH and DNA hypermethylation and an advanced cancer stage or a poor cancer prognosis. As such, Kondo cannot anticipate claim 20 or 23.

In view of the foregoing, claims 13, 15, 17, 20, and 23 are novel over Kondo. Claims 22 (dependent from claim 20) and 25 (dependent from claim 23) are not

anticipated by Kondo for at least the same reasons. Applicants respectfully request that the rejections be withdrawn.

(3) Claims 1 and 7-12 are rejected as being anticipated by Hoon et al. (WO 96/29430; "Hoon").

Amended claim 1 is directed to a method of detecting DNA markers in a cell-free bone marrow sample from a subject, wherein the DNA markers are indicative of LOH, hypermethylation, or mutation in KRAS or BRAF gene. Amended claim 7 is directed to a method of detecting cancer by detecting one or more DNA markers in a cell-free bone marrow sample from a subject, wherein LOH or hypermethylation of the markers is indicative of cancer in the subject, or wherein the markers include KRAS or BRAF, and mutation of the markers is indicative of cancer in the subject. Claim 9 is directed to a method of staging cancer by detecting one or more DNA markers in a cell-free bone marrow sample from a subject suffering from cancer, wherein LOH, hypermethylation, or mutation of the markers is indicative of an advanced stage of the cancer in the subject. Claim 11 is directed to a method of prognosing cancer by detecting one or more DNA markers in a cell-free bone marrow sample from a subject suffering from cancer, wherein LOH, hypermethylation, or mutation of the markers is indicative of a poor prognosis of the cancer in the subject. All these claims involve DNA markers of LOH, hypermethylation, or mutation. In contrast, Hoon discloses detection of nucleic acids corresponding to multiple melanoma- or breast cancer-specific markers using template-dependent amplification processes (Abstract). It discloses no DNA markers of LOH, hypermethylation, or mutation, and therefore cannot anticipate claim 1, 7, 9, or 11. By the same token, claims 8 (depend from claim 7), 10 (dependent from claim 9), and 12 (dependent from claim 11) are also novel over Hoon. Withdrawal of the rejections is respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 103

(1) Claims 2-3 and 5-6 are rejected as being unpatentable over Hoon in view of Anker et al. (1999) Cancer and Metastasis Reviews 18:65-73 ("Anker"). Claims 3 and 6 have been canceled without prejudice and will not be discussed below.

Amended claim 1 is directed to a method of detecting DNA markers in a cell-free bone marrow sample, wherein the DNA markers are indicative of LOH, hypermethylation, or mutation in KRAS or BRAF gene.

In contrast, Hoon discloses detection of nucleic acids corresponding to multiple melanoma- or breast cancer-specific markers using template-dependent amplification processes in biological samples such as bone marrow samples (Abstract; page 5, lines 28-33). It discloses no DNA markers of LOH, hypermethylation, or mutation. Anker, on the other hand, describes detection of circulating tumor DNA in the blood (plasma/serum) of cancer patients (Title). It mentions the finding of N-ras mutations in DNA extracted from the bone marrow of patients with myelodysplastic syndrome and acute myelogenous leukaemia (AML) (page 68, left column, lines 35-40). Since neither Hoon nor Anker teaches DNA markers indicative of LOH, hypermethylation, or mutation in KRAS or BRAF gene in a cell-free bone marrow sample, the two references, either alone or in combination, cannot render claim 1 obvious because they do not add up to the method of claim 1.

Further, it is well known in the art that each gene has a unique pattern, the presence of LOH, DNA hypermethylation, or DNA mutation in one type of sample (e.g., blood plasma or serum) does not reasonably predict the presence of the LOH, DNA hypermethylation, or DNA mutation in another type of sample (e.g., cell-free bone marrow), and the presence of mutation in one gene in a sample (e.g., mutation

in N-ras in a bone marrow sample) does not reasonably predict the presence of mutation in another gene in the same sample (e.g., mutation in KRAS or BRAF in a bone marrow sample). Therefore, even if one skilled in the art would have been motivated to combine Hoon and Anker, there would not have been reasonable expectation of success in detecting DNA markers indicative of LOH, hypermethylation, or mutation in KRAS or BRAF gene in a bone marrow sample.

In view of the foregoing, claim 1 is non-obvious over Hoon and Anker. Claims 2 and 5, dependent from claim 1, are also patentable over the cited art for at least the same reasons. Applicants respectfully request that the rejections be withdrawn.

(2) Claim 4 is rejected as being unpatentable over Hoon in view of Fujiwara et al. (1999) Cancer Research 59:1567-1571 ("Fujiwara").

As mentioned above, amended claim 1 requires detection in a cell-free bone marrow sample of DNA markers indicative of LOH, hypermethylation, or mutation. While Hoon discloses detection of nucleic acids corresponding to multiple melanoma- or breast cancer-specific markers using template-dependent amplification processes in biological samples such as bone marrow samples, it discloses no DNA markers of LOH, hypermethylation, or mutation. Fujiwara, on the other hand, describes detection of LOH in the plasma of blood and melanoma tissues (page 1567, left column, Abstract; page 1568, left column, lines 2-17). Since neither Hoon nor Fujiwara teaches DNA markers indicative of LOH, hypermethylation, or mutation in a cell-free bone marrow sample, the two references, either alone or in combination, cannot render claim 1 obvious because they do not add up to the method of claim 1.

Further, as mentioned above, it is well known in the art that the presence of LOH in one type of sample (e.g., blood plasma or tumor tissue) does not reasonably predict the presence of the LOH in another type of sample (e.g., cell-free bone

marrow). Therefore, even if one skilled in the art would have been motivated to combine Hoon and Fujiwara, there would not have been reasonable expectation of success in detecting DNA markers indicative of LOH in a bone marrow sample.

In view of the foregoing, claim 1 is non-obvious over Hoon and Fujiwara. Claim 4, dependent from claim 1, is also patentable over the cited art for at least the same reasons. Applicants respectfully request that the rejections be withdrawn.

(3) Claim 16 is rejected as being unpatentable over Kondo in view of Anker.

Amended claim 16 is directed to a method of detecting a combination of LOH and DNA hypermethylation in a sample from a subject, wherein the DNA hypermethylation is detected in RASSF1A, MGMT, GSTP1, RAR-ß, TWIST, APC, DAPK, or Cyclin D2 promoter.

In contrast, while Kondo describes detection of LOH and DNA hypermethylation in non-cancerous and cancerous liver tissue samples, it does not disclose specifically the combination of LOH and DNA hypermethylation in RASSF1A, MGMT, GSTP1, RAR-ß, TWIST, APC, DAPK, or Cyclin D2 promoter (page 976, left column, Table 5). Anker, on the other hand, describes detection of aberrant methylation of the MGMT promoter in tumors and serum of non-small-cell lung cancer patients (page 68, right column, lines 13-27). However, it does not suggest at all a combination of LOH and DNA hypermethylation. It is Applicants' unexpected discovery that the combination of LOH and DNA hypermethylation in gene promoters (including the MGMT gene promoter) provides a more sensitive cancer diagnostic method. See, e.g., page 68, line 24 – page 69, line 24 of the specification. Neither Kondo nor Anker suggests such a method. Therefore, absent Applicants' discovery, Kondo and Anker, either alone or in combination, would not

have motivated one skilled in the art to combine LOH with DNA hypermethylation in the MGMT promoter to come up with the method of claim 16.

In view of the foregoing, Applicants submit that claim 16 is non-obvious over Kondo and Anker. Withdrawal of the rejections is respectfully requested.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned at the Los Angeles, California telephone number (310) 785-4600 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Dated: November 26, 2007

By: _____

Y. Jenny Luo, Ph.D.
Registration No. 54,284
Patent Agent for Applicants

1999 Avenue of the Stars, Suite 1400
Los Angeles, California 90067
Telephone: 310-785-4600
Fax: 310-785-4601